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Attention of
Robert Watson

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RJW/6282743		FOR FURTHER ACTION		See Form PCT/PEA416
International application No. PCT/GB2005/000768		International filing date (day/month/year) 01.03.2005		Priority date (day/month/year) 01.03.2004
International Patent Classification (IPC) or national classification and IPC C07D487/04, C07D519/00, A61K31/5517, A61P35/00				
Applicant SPIROGEN LIMITED				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau a total of 8 sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand 23.12.2005		Date of completion of this report 01.03.2006		
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80299 Munich Tel. +49 89 2399 - 0 Tx: 523656 apmu d Fax: +49 89 2399 - 4465		Authorized Officer Cortés, J Telephone No. +49 89 2399-8206		



INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2005/000768

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-74 as originally filed

Claims, Numbers

1-10 as originally filed

11-34 received on 23.12.2005 with letter of 22.12.2005

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**International application No.
PCT/GB2005/000768**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial
applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 23

because:

☒ the said international application, or the said claims Nos. 23 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**International application No.
PCT/GB2005/000768

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-10,24-34
	No: Claims	11-23
Inventive step (IS)	Yes: Claims	
	No: Claims	1-34
Industrial applicability (IA)	Yes: Claims	1-22, 24-34
	No: Claims	

2. Citations and explanations (Rule 70.7):**see separate sheet**

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and /or

2. Non-written disclosures (Rule 70.9)**see separate sheet**

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/GB2005/000768**Re Item III****Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Due to the term "prodrugs" the present claims 11-20 encompass so many known compounds that it was not possible to cite all documents relevant to the issue of novelty. Therefore only some exemplary documents have been cited.

Claim 23 relates to subject matter considered by this Authority to be covered by the provisions of rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims (article 34(4)(a)(i) PCT).

Re Item V**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

The following documents have been cited in the International Search Report:

- D1: CHEN ET AL: "A novel approach to the synthesis of cytotoxic C2?C3 unsaturated pyrrolo[2,1-c][and]benzodiazepines (PBDs) with conjugated acrylyl C2-substituents" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 14, no. 6, 27 February 2004 (2004-02-27), pages 1547-1550, XP002329273
- D2: KANG ET AL: "Synthesis of a novel C2-aryl substituted 1,2-unsaturated pyrrolobenzodiazepine" CHEMICAL COMMUNICATIONS, vol. 14, 11 June 2003 (2003-06-11), pages 1688-1689, XP002329274
- D3: GREGSON ET AL: "Synthesis of the first examples of A-C8/C-C2 amide-Linked pyrrolo[2,1-c][1,4]benzodiazepine dimers" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 13, no. 14, 31 March 2003 (2003-03-31), pages 2277-2280, XP002329063
- D4: COOPER ET AL: "Synthesis of novel C2-aryl pyrrolobenzodiazepines (PBDs) as potential antitumour agents" CHEMICAL COMMUNICATIONS, vol. 16, 5 July 2002

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/GB2005/000768

(2002-07-05), pages 1764-1765, XP002329275

- D5: GREGSON ET AL: "Synthesis of the first example of a c2-C3/C2?-C3?-endo unsaturated pyrrolo[2,1-c][1,4]benzodiazepine dimer" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 11, no. 21, 27 August 2001 (2001-08-27), pages 2859-2862, XP002329276
- D6: GREGSON ET AL: "Effect of C2/C3-endo unsaturation on the cytotoxicity and dna-binding reactivity of pyrrolo[2,1-c][1,4]benzodiazepines" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 10, no. 16, 14 April 2000 (2000-04-14), pages 1849-1852, XP004216014
- D7: WO 00/12508 A (THE UNIVERSITY OF PORTSMOUTH HIGHER EDUCATION (GB)) 9 March 2000 (2000-03-09)
- D8: FUKUYAMA ET AL: "Total synthesis of (+)-porothramycin B" TETRAHEDRON LETTERS, vol. 34, no. 16, 16 April 1993 (1993-04-16), pages 2577-2580, XP002135999

Novelty (Article 33(2) PCT)

D1 to D8 disclose compounds which are potential "prodrugs" of the compounds of formula III and are therefore within the scope of claims 11-20. The matter of claims 11 to 23 is therefore not novel.

The Applicant alleges in his letter of 22.12.2005 that the compounds of claims 11 and 14 differ from the prior art compounds in that both the N10 and C11 hydroxy positions are protected.

This is not correct, the hydroxy "unprotected" prior art compounds are potential "prodrugs" of the compounds of present formula III, since they will be transformed in-vivo to their e.g. acyl derivatives.

The compounds of claim 1 differ from the compounds in D1 in the oxygen protecting group

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R11 (claim 1 does not encompass "prodrugs" since they are intermediates and not active principles). Claims 1-10 and 24-34 are therefore novel.

Inventive Step (Article 33(3) PCT)

The problem of claims 1-10 and 24-34 was the provision of a new process and new intermediates for the preparation of compounds of claim 11. D1 could be regarded as the closest prior art.

The present process of claim 31 and the present intermediates of claim 1 are analogous to the process and intermediates which have already been disclosed in D1. The present intermediates differ only in the use of an oxygen-protecting group R11. The use of oxygen-protecting groups is an obvious measure for a skilled person.

Therefore the present claims 1-10 and 24-34 lack an inventive step.

The problem of claims 11-23 was the provision of new compounds for the treatment of proliferative diseases. D1 could be regarded as the closest prior art. Since the compounds as well as their pharmacology are well known from D1-D8, the matter of claims 11-23 also lacks an inventive step.

New compounds of claims 11-23 might differ from structurally related prior art compounds in D1-D8 in that both the N10 and C11 hydroxy positions are protected. The provision of hydroxy protected derivatives of known pharmacologically active compounds is not regarded as an activity based on an inventive step.

The Applicant argues in his letter of 22.12.2005 that the present C11 hydroxy protected intermediates have an advantage when compared with the compounds in D1, which are C11 hydroxy "unprotected", since such intermediates can be used in a wider range of synthesis, e.g. of Stille and Suzuki coupling, for preparing a wider range of C2-derivatives.

This is true, but the use of hydroxy protecting groups in reactions which are known to be incompatible with a free hydroxy group is an obvious measure for a skilled person.

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The Applicant further argues that the compounds of claim 14 are inventive over the structurally closest related compounds in D5 because the C2 aryl substituent. The Applicant provides data which show an increased activity of a C2 aryl substituted test compound when compared to a C2 unsubstituted reference compound of D5. The first problem is that the test compound is not a compound according to the present invention, since it is unsubstituted at the N10 and C11 positions and has a N10=C11 double bond. The second problem is that a unitary group of inventions must have a common inventive concept, i.e. a common distinctive feature. According to the Applicant this special technical feature is the C11 protective group. In order to establish an inventive step, the Applicant should have made credible by means of comparative data, that this C11 protective group has an effect on the pharmacological activity of the final compounds.

Re Item VI**Certain documents cited**

Reference is made to the following P-documents:

D9: WO 2004/043963 A (SPIROGEN (GB)) 27 May 2004 (2004-05-27)

D10: TIBERGHEN ET AL: "Application of the Stille coupling reaction to the synthesis of C2-substituted endo-exo unsaturated pyrrolo[2,1-c][1,4]benzodiazepines (PBDs)" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 14, no. 20, 1 September 2004 (2004-09-01), pages 5041-5044, XP002329277

The priority documents pertaining to the present application were not available at the time of establishing this report. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, D9 and D10 could become relevant to assess whether the present claims satisfy the criteria set forth in Article 33(1) PCT.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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York House
23 Kingsway
London Greater London WC2B 6HP
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (PCT Rule 71.1)

Date of mailing
(day/month/year)

01.03.2006

Applicant's or agent's file reference
RJW/6282743

IMPORTANT NOTIFICATION

International application No.
PCT/GB2005/000768

International filing date (day/month/year)
01.03.2005

Priority date (day/month/year)
01.03.2004

Applicant
SPIROGEN LIMITED

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

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